VARIATION IN COVID-19 INFECTION PARAMETERS ENDORSE THE CALL FOR GREATER EFFORTS IN PERSONALISED MEDICINE

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Abstract: New data on several COVID-19 infection parameters are slowly beginning to emerge which include the relative frequencies of symptomatic *versus* asymptomatic individuals positive for COVID-19, individual variation in response to re-purposed drug treatments, prognostic factors for developing severe COVID-19 and genetic risk factors for COVID-19 susceptibility and severity. From a larger perspective, it is our view that these parameters endorse the call for greater efforts in personalised medicine, especially when specific pharmacological interventions (i.e. vaccines or drugs to COVID-19 and other zoonotic diseases) are yet to be developed. Here, the aim of personalised medicine would be to rapidly identify vulnerable individuals and subsequently to design better treatment regimens for them, should COVID-19 or other pandemics appear in future. Application of genomic technology also will continue to be of importance to gain knowledge about the biology of the virus and will facilitate vaccine development and predict markers of resistance and/or susceptibility.

Keywords: COVID-19, personalised medicine, susceptibility markers, genetic variants

Abbreviations: Coronavirus disease 19 (COVID-19), severe acute respiratory syndrome coronavirus (SARS-CoV-2).

Introduction

As of June 2020, most parts of the world have now been affected by an outbreak of coronavirus disease (the COVID-19 pandemic). Border control, quarantine processes, social distancing, personal hygiene, population testing, and contact tracing have all been adopted as global strategies to slow down and eliminate virus transmission (WHO, 2020a). In many countries, social distancing was mandated and strict movement control orders and/or total lockdowns were put in place (Mat *et al.,* 2020).

Nonetheless, at the time of writing this report, more than 6 million COVID-19 cases and 300,000 deaths have been recorded, globally (WHO, 2020b). However, infection rates are declining in some countries (e.g., Malaysia, New Zealand, Taiwan and South Korea) while in others (e.g., the United States, Brazil, India and the United Kingdom) they continue to rise (WHO, 2020b).

It is perhaps surprising, if not alarming, that in many of the latter countries' controls are presently being relaxed. In contrast, the lessons learned in Spain and Italy show how effective tight population controls can be even when there is widespread person-to-person transmission (Saez *et al.,* 2020; Saglietto *et al.,* 2020; WHO, 2020b).

Whatever the case is, the objectives of any mitigation strategies are:

1) to spare the lives of vulnerable people – those with diabetes, respiratory problems, compromised immunity or just over 70 years old,

2) to reduce the number of serious cases to a level that health services can cope with, and

3) to eliminate community transmission and later cross border transmission. Some administrations have managed this well, but

others (notably the UK and US) have not. Indeed, some countries have taken a laissez-faire approach and opted early to have few restrictions in the hope of attaining a "herd immunity". This can be said to have had fairly disastrous consequences, especially in the UK, Sweden and Brazil (Korhonen & Granberg, 2020; Lancet, 2020; Paital *et al.,* 2020). Even in countries where COVID-19 rates are low, public health officials must remain vigilant to prevent a second wave of infections as was the reported experiences in China and South Korea (Xu & Li, 2020). These concerns will only increase as cross-border travel begins again.

In this regard, political and diplomatic decisions are especially complex. Opening one's borders to another country has the de facto effect of opening them to all the other countries that one's new partner has (or will develop) mutual travel agreements with.

COVID-19 Infection Parameters and the Call for Personalised Medicine

New data on several COVID-19 infection parameters are slowly beginning to emerge and should become important resources for COVID-19 researchers. These include relative frequencies of symptomatic *versus* asymptomatic individuals positive for COVID-19, individual variation in response to re-purposed drug treatments (e.g., chloroquine and hydroxychloroquine), prognostic factors for developing severe COVID-19 (underlying medical conditions and age) and genetic risk factors for COVID-19 susceptibility and severity (Cohen, 2020; Dai, 2020; Gémes *et al.,* 2020; Sanchez-Mazas, 2020; WHO, 2020; Zhao *et al.,* 2020).

From a larger perspective, it is our view that these parameters endorse the call for greater efforts in personalised medicine, especially when specific pharmacological interventions (i.e. vaccines or drugs to COVID-19 and other zoonotic diseases) are yet to be developed. The era of 'one-size-fits-all' medicine seems to be no longer sufficient for disease prevention and treatment, as demonstrated in the global struggle to control, diagnose, and treat COVID-19 patients.

In principle, the opportunity now exists for personalised medicine to be more widely adopted with genomic-scale information from patients used for disease screening and treatment, including for prescription of drugs or surgery.

Already a huge body of evidence shows associations between genetic variants in the human genome and susceptibility or resistance towards diseases (Chambers *et al.,* 2016; Hoffmann, 2018; Haydar *et al.,* 2019; Lalrohlui *et al.,* 2020; Nicholls *et al.,* 2020; Sanchez-Mazas, 2020).

Variations in immune gene coding for human leukocyte antigens (HLA), cytokines and killer cell immunoglobulin-like receptors (KIRs) and in many other regions of human genome have now been implicated in serious medical conditions including autoimmune diseases, microbial infections, and cancer development (Edinur *et al*., 2016; Norhalifah *et al*., 2018; Saleh *et al*., 2018; Tao *et al*., 2020).

For example, *HLA-B*27* is associated with the occurrence of ankylosing spondylitis and uveitis, while *HLA-DRB1*04* has been linked to rheumatoid arthritis (Edinur *et al*., 2013). There are similar findings for other genetic regions where combinatorial interactions between KIR and its HLA ligands may serve to either increase the risk of disease or offer a better prognosis; e.g. *KIR2DL1-C2*$^+$*HLA-C* in predisposition to preeclampsia and *KIR2DL3-C1*$^+$*HLA-C* in susceptibility to HCV infection, respectively (Nemat-Gorgani *et al*., 2014; Tao *et al*., 2020).

Hence, taken overall many diseases that have now been linked to specific regions in human genome. Advances in molecular technology provide further motivation for a wider application of personalised medicine in our healthcare systems.

In addition, people belonging to particular ethnicities are much more likely to be affected by a characteristic range of diseases. This is because there are differences in frequency distributions of susceptibility markers in people with

different genetic lineages (Edinur *et al.,* 2012; Bentley *et al.,* 2020).

For example, the native Hawaiians (and possibly their other 350 million Austronesian relatives that are widespread across the wider Asia Pacific region) were reported to have elevated risk from COVID-19. Variants in the *APOL1* gene that are associated with kidney diseases are frequently detected in populations with African ancestry (Norhalifah *et al.,* 2016; Bentley *et al.,* 2020; Chambers & Edinur, 2020; Murray *et al.,* 2020).

Therefore, inclusion of people with different ancestries in this new push for widespread genetic screening will not only avoid disparity in health care services but could also optimize the effectiveness and accuracy of personalised medicine in clinical practice. Attention should equally be given to pharmacogenomics of drug response to make sure that any new drugs and their dosages are fully tailored to best suit people of different genetic backgrounds (Roden & George Jr., 2002)

Advances in molecular biology including whole genome sequencing or single nucleotide polymorphism chip array technologies provide good platforms for personalised medicine. These latest molecular technologies have the power to quickly gather huge amounts of genomic information at a relatively low cost. Thus, they are perfectly positioned to become a key part in strategic preparedness and response planning for the current COVID-19 outbreak and future pandemics.

It is equally important to note that whole genome sequencing technology was also used to characterize the genome of severe acute respiratory syndrome coronavirus (SARS-CoV-2), the virus that was responsible for the massive spread of COVID-19. This took just one week after it was first isolated from clusters of pneumonia patients in Wuhan, China (WHO, 2020b). This effort needs to be maintained as the virus continues to accumulate mutational changes giving rise to new strains (Lokman *et al.,* 2020).

Conclusion

As COVID-19 continues to spread across the world, its progress has revealed the failure of some social control strategies to effectively contain disease spread and a less than optimal ability to provide treatment for affected individuals, much as recorded for other previous pandemics (LePan, 2020). Personalised medicine can thus become one important new element in an improved pro-active approach. Here, the aim would be to rapidly identify vulnerable individuals and subsequently to design better treatment regimens for them, should COVID-19 or other pandemic appear in future.

The application of genomic technology also will continue to be of importance to gain knowledge about the biology of the virus and will facilitate vaccine development and predict markers of resistance and/or susceptibility. Personalised medicine should thus become a major goal for modern medicine and run in parallel with one of the seventeen Sustainable Development Goals (SDGs) adopted by United Nations to fight against infectious diseases and provide universal health coverage (United Nations, 2019).

Acknowledgements

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